(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
15 May 2003 (15.05.2003)

PCT

(10) International Publication Number
WO 03/039597 A1

(51) International Patent Classification[7]: A61K 41/00, 47/08, 47/10, 31/40, A61P 17/14

(21) International Application Number: PCT/CA02/01734

(22) International Filing Date:
8 November 2002 (08.11.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/338,295 9 November 2001 (09.11.2001) US

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(81) Designated States *(national)*: AE, AG, AL, AM, AT (utility model), AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ (utility model), CZ, DE (utility model), DE, DK (utility model), DK, DM, DZ, EC, EE (utility model), EE, ES, FI (utility model), FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SI, SK (utility model), SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 03/039597 A1

(54) Title: COMPOSITIONS COMPRISING A PHOTOSENSITIZER AND A SKIN-PENETRATION ENHANCER AND THEIR USE IN PHOTODYNAMIC TREATMENT

(57) Abstract: The present invention relates to a composition comprising a photosensitizing agent and a skin-penetration enhancer. The composition herein show improved delivery of the photosensitizer through the stratum corneum. In addition, the composition of the present invention show improved stability and a reduced incidence of skin photosensitivity.

COMPOSITIONS COMPRISING A PHOTOSENSITIZER AND A SKIN-PENETRATION ENHANCER AND THEIR USE IN PHOTODYNAMIC TREATMENT

Technical Field

The present invention relates to a composition comprising photosensitizing agents.

Background to the Invention

Photodynamic therapy is a diverse field of medical treatment. Generally, PDT involves the delivery of a photosensitizer to the target tissue and, subsequently, irradiating the target area with light of an appropriate wavelength to activate the PS. This activation results in an agent that modifies or destroys the target tissues. The PS is usually delivered systemically although it has been proposed to deliver it locally.

Local delivery has the advantage that the PS is delivered directly to the target tissue and, consequently, high concentrations of the drug in the target tissue can be achieved. However, local delivery also has some disadvantages. Photosensitizing agents do not easily penetrate the stratum corneum. In addition, the PS agents are relatively reactive so it is difficult to formulate a stable composition.

At the time of writing, one product that is marketed for topical PDT is Levulan® Kerastick®. This product is used for the treatment of non-hyperkeratotic actinic keratosis lesions on the face or scalp. The photosensitizer in this product is a pro-drug and is converted into the active *in situ*. The product is supplied in a plastic applicator tube containing two sealed glass ampules. One ampule contains the a solution to act as the vehicle and the other the photosensitizing agent as a dry solid. The applicator tube is enclosed in a protective cardboard sleeve and cap. Immediately prior to application, the two ampules are crushed and the solution is mixed with the photosensitizer. The contents are then shaken for several minutes until the drug is dissolved. The solution containing dissolved drug must be discarded two hours after mixing due to the short stability of the product

Thus there remains a need for a stable photosensitizer composition suitable for topical application to the skin.

It has also been found that topical photosensitizer compositions can cause skin-photosensitivity reactions. In addition, it has been problematic to deliver the photosensitizer to the correct target tissue because often the stratum corneum is difficult to penetrate.

Summary of the Invention

The present invention relates to a composition comprising a photosensitizing agent and at least one skin-penetration enhancer. The compositions herein show improved delivery of the photosensitizer through the stratum corneum. In addition, the compositions of the present invention show improved stability.

The photosensitizers of the present compositions are able to penetrate the stratum corneum. Consequently, when light energy is delivered, the photosensitizer is activated at the target tissue rather than at the surface. This means that the compositions are more efficacious. In addition, it has surprisingly been found that, when using the compositions of the present invention, administration of light does not cause substantial skin photosensitivity. While not wishing to be bound by theory, it is thought that this the fact that the photosensitizer distributes to the epidermis, rather than in the dermis, means there is less skin photosensitivity.

Unless otherwise specified, all documents referred to are incorporated herein by reference.

Unless otherwise specified, all percentages herein are expressed as weight percentages.

Detailed Description

The present invention provides compositions comprising a photosensitizing agent and a skin penetration enhancer. These elements will be described in more detail below.

The compositions of the present invention are preferably substantially free of water. As used herein, the term "substantially free of water" means that the composition comprises less than about 5%, preferably less than about 3%, by weight, of free water. It is preferred that the compositions herein do not have a total water content (i.e. free water plus any water of hydration) of more than about 15%, preferably less than about 10%.

Photosensitizer

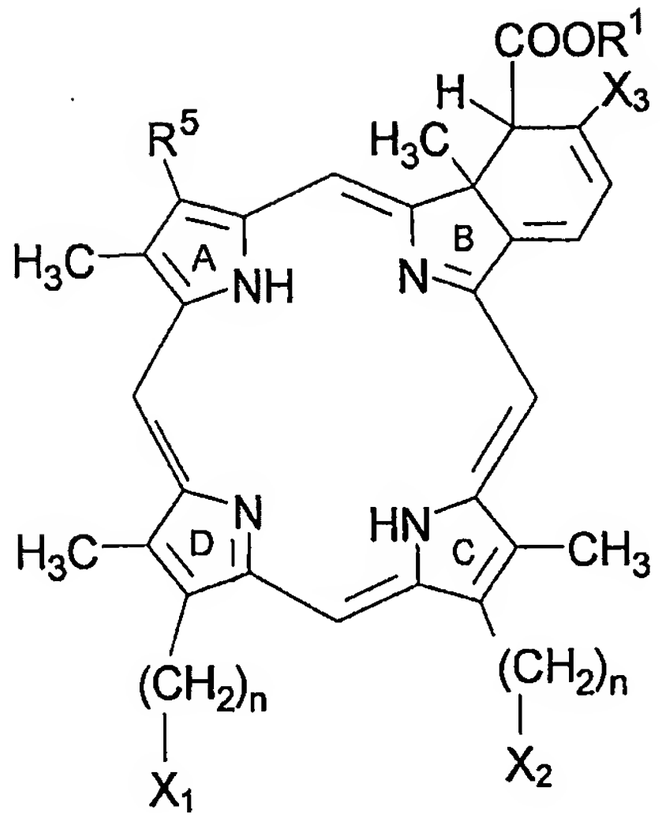
Any suitable photosensitizing agent may be used herein. Generally, these will absorb radiation in the range of from 400nm to 800nm, typically from 600nm to 750nm.

As used herein, "photosensitizer" or "photosensitizing agent" means a chemical compound which, when accumulated in selected target tissues and contacted by radiation, absorbs the light and induces changes to, or destruction of, the target. Virtually any chemical compound that ca be taken up by target cells or tissues and absorbs light may be used in this invention. Preferably, the chemical compound is nontoxic to the animal to which it is administered or is capable of being formulated in a nontoxic composition. Preferably, the chemical compound in its photodegraded form is also nontoxic. A listing of photosensitive chemicals may be found in Kreimer-Birnbaum, Sem. Hematol. 26:157-73, 1989 (incorporated herein by reference) and in Redmond and Gamlin, Photochem. Photbiol. 70 (4): 391-475 (1999).

In preferred embodiments of the invention, the photosensitizer is selected from a particularly potent group of photosensitizers known as green porphyrins, which are described in detail in U.S. Patent No. 5,171,749 (incorporated herein by reference). The term "green porphyrins" refers to porphyrin derivatives obtained by reacting a

porphyrin nucleus with an alkyne in a Diels-Alder type reaction to obtain a mono-hydrobenzoporphyrin. Such resultant macropyrrolic compounds are called benzoporphyrin derivatives (BPDs), which is a synthetic chlorin-like porphyrin with various structural analogues, as shown in U.S. Patent 5,171,749. Typically, green porphyrins are selected from a group of tetrapyrrolic porphyrin derivatives obtained by Diels-Alder reactions of acetylene derivatives with protoporphyrin under conditions that promote reaction at only one of the two available conjugated, nonaromatic diene structures present in the protoporphyrin-IX ring systems (rings A and B). Metallated forms of a Gp, in which a metal cation replaces one or two hydrogens in the center of the ring system, may also be used in the practice of the invention. The preparation of the green porphyrin compounds useful in this invention is described in detail in U.S. Patent No. 5,095,030 (hereby incorporated by reference).

Preferably, the BPD is a benzoporphyrin derivative diester di-acid (BPD-DA), mono-acid ring A (BPD-MA), mono-acid ring B (BPD-MB), or mixtures thereof. These compounds absorb light at about 692nm wavelength and have improved tissue penetration properties. The compounds of formulas BPD-MA and BPD-MB may be homogeneous, in which only the C ring carbalkoxyethyl or only the D ring carbalkoxyethyl would be hydrolyzed, or may be mixtures of the C and D ring substituent hydrolyzates. A number of other BPD B-ring derivatives may also be used in the present methods. These derivatives have the following general formula:



wherein; R^5 is vinyl, R^1 and R^6 are methyl, and n is 2. X_1, X_2, and X_3 are listed in the tables below:

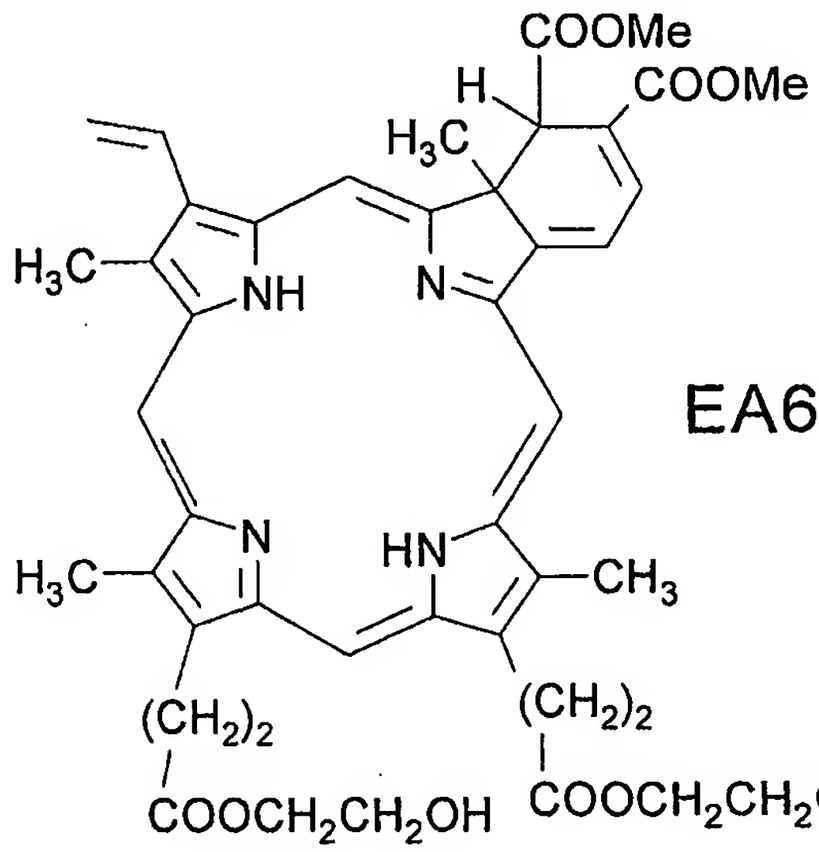
Table 1. Hydrophilic BPD B-ring analogs

Drug	X_1	X_2	X_3
QLT0061	COOH	COOH	COOH
QLT0077	$CONH(CH_2)_2N^+(CH_3)_3I^-$	$CONH(CH_2)_2N^+(CH_3)_3I^-$	$COOCH_3$
QLT0079	$CONH(CH_2)_2N^+(CH_3)_2((CH_2)_3CH_3$	$CONH(CH_2)_2N^+(CH_3)_2((CH_2)_3CH_3)$	$COOCH_3$
QLT0086	$CONHCH(COOH)CH_2COOH$	$CONHCH(COOH)CH_2COOH$	$COOCH_3$
QLT0092	$CONH(CH_2)_2NH(CH_3)_2$ CF_3COO^-	$CONH(CH_2)_2NH(CH_3)_2$ CF_3COO-	$COOCH_3$
QLT0094	$CONHCH_2COOH$	$CONHCH_2COOH$	$CONHCH_2COOH$

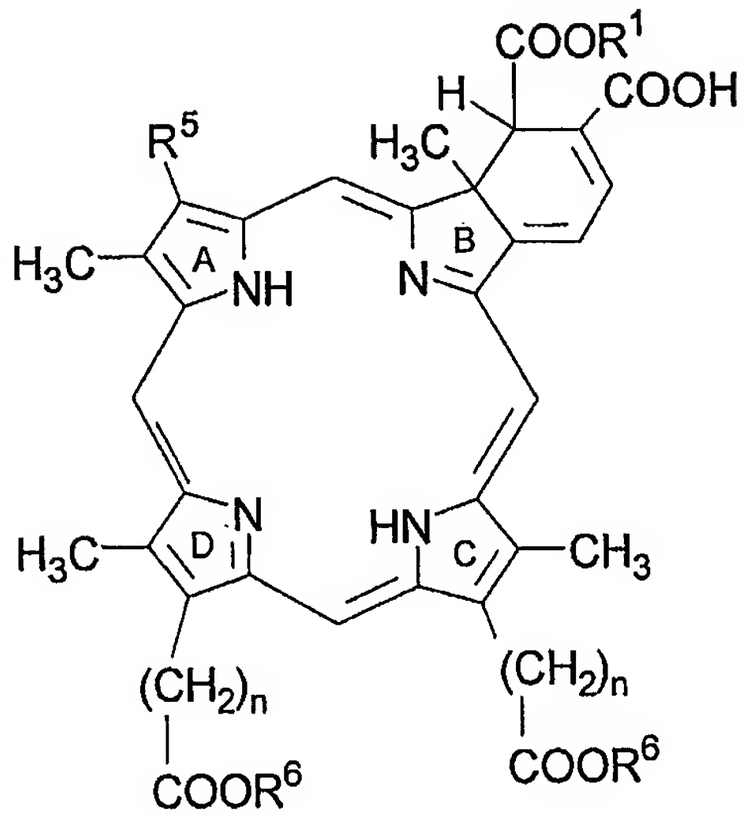
Table 2. Lipophilic BPD B-ring analogs

Drug	X1	X2	X3
QLT0060	$CO(O(CH_2)_2)0H$	$CO(O(CH_2)_2)0H$	$COOCH_3$
QLT0069	$COOCH_3$	$COOCH_3$	COOH
QLT0074	$CO(OCH_2CH_2)0H$	$CO(OCH_2CH_2)0H$	$COOCH_3$
QLT0078	$CO(O(CH_2)_2)_20H$	$CO(O(CH_2)_2)_20H$	$COOCH_3$
QLT0080	$CO(O(CH_2)_2)_3OH$	$CO(O(CH_2)_2)_3OH$	$COOCH_3$
QLT0081	$CO(O(CH_2)_2)_2OCH_3$	$CO(O(CH_2)_2)_2OCH_3$	$CO(O(CH_2)_2)_2OCH_3$
QLT0082	$CO(O(CH_2)_2)_2OH$	$CO(O(CH_2)_2)_2OH$	$CO(O(CH_2)_2)_2OH$
QLT0083	$CO(O(CH_2)_2)_3OH$	$CO(O(CH_2)_2)_3OH$	$CO(O(CH_2)_2)_3OH$
QLT0087	$CO(O(CH_2)_2)_4OH$	$CO(O(CH_2)_2)_4OH$	$COOCH_3$
QLT0088	$COOCH_3$	$COOCH_3$	$CONH(C_6H_4)(C_5H_{10}N)$
QLT0090	$CO(O(CH_2)_2)_5OH$	$CO(O(CH_2)_2)_5OH$	$COOCH_3$
QLT0093	$CO(O(CH_2)_2)_5OH$	$CO(O(CH_2)_2)_5OH$	$CO(O(CH_2)_2)_5OH$

Preferred photosensitizers are the benzoporphyrin derivative mono-acid (BPD-MA), EA6, also known as QLT 0074, (as set forth in U.S.5,929,105) and B3 (as set forth in U.S. Pat. No. 5,990,149). BPD-MA, for example, is lipophilic and a potent photosensitizer. EA6 and B3 have the following structures:



EA6



wherein; R^5 is vinyl, R^1 and R^6 are methyl, and n is 0, 1, 2, or 3. Preferably, n is 2.

Additionally, the photosensitizers used in the invention may be conjugated to various ligands to facilitate targeting. These ligands include receptor-specific ligands as well as immunoglobulins and fragments thereof. Preferred ligands include antibodies in general and monoclonal antibodies, as well as immunologically reactive fragments of both.

Dimeric forms of the green porphyrin and dimeric or multimeric forms of green porphyrin/porphyrin combinations can be used. The dimers and oligomeric compounds of the invention can be prepared using reactions analogous to those for dimerization and oligomerization of porphyrins *per se*. The green porphyrins or green porphyrin/porphyrin linkages can be made directly, or porphyrins may be coupled, followed by a Diels-Alder reaction of either or both terminal porphyrins to convert them to the corresponding green porphyrins. Of course combinations of two or more photosensitizers may be used in the practice of the invention.

In addition to the above mentioned preferred photosensitizing agents, additional examples of photosensitizers useful in the invention include, but are not limited to, green porphyrins disclosed in US Pat. Nos. 5,283,255, 4,920,143, 4,883,790, 5,095,030, and 5,171,749; and green porphyrin derivatives, discussed in US Pat.

Nos. 5,880,145 and 5,990,149. Several structures of typical green porphyrins are shown in the above cited patents, which also provide details for the production of the compounds.

The amount of photosensitizer used herein will depend on a variety of factors such as the specific type of PS and the type of activation energy source. However, it is preferred that the compositions herein comprise from about 0.0001% to about 50%, more preferably from about 0.001% to about 5%, even more preferably from about 0.01% to about 2%, still more preferably from about 0.1% to about 1%, by weight, of photosensitizer.

Skin-Penetration Enhancer

The compositions herein must comprise a skin-penetration enhancer. As used herein, the term "skin-penetration enhancer" means a substance or mixture of substances that aids in the delivery of the photosensitizing agent through the Stratum Corneum of the skin.

Any skin-penetration enhancer suitable for aiding the delivery of the photosensitizing agent can be used herein. A list of skin-penetration enhancers can be found in "Pharmaceutical Skin Penetration Enhancement" (1993) Walters, K.A., ed.; Hadgraft, J., ed - New York, N.Y. Marcel Dekker and in "Skin Penetration Enhancers cited in the Technical Literature" Osbourne, D.W. Pharmaceutical Technology, November 1997, pp 59-65, both of which are incorporated herein by reference. Highly preferred for use in the compositions herein are hydrophobic skin-penetration enhancers.

Preferred skin-penetration enhancers are selected from glycol ethers, fatty acids, fatty acid esters, glycol esters, glycerides, azones, polysorbates, alcohols, dimethylsulfoxide, and mixtures thereof.

Preferred skin-penetration enhancers for use herein include, but are not limited to, diethylene glycol monoethyl ether (Transcutol®), Oleyl alcohol, Oleic acid, Azone (Laurocapram or 1-n-Dodecyl azacycloheptan-2-one), Propylene glycol mono- and

diesters of fats and fatty acids (e.g. propylene glycol monocaprylate, propylene glycol monolaurate), Triglycerides and lipids (e.g. linoleic acid), Macrogolglycerides or Polyethylene glycol glycerides and fatty esters (e.g. stearoyl macrogolglycerides, oleoyl macrogolglycerides, lauroyl macrogolglycerides, Oleyl macrogol-6-glycerides, Lauroyl macrogol-6 glycerides), Glycerides and fatty acid esters of polyethylene glycol (e.g. caprylocaproyl macrogolglycerides, capryl-caproyl macrogolglycerides, oleoyl macrogolglycerides), Polyoxyl 40 Hydrogenated Castor Oil (Cremophor RH 40), Polysorbate 80 (Tween 80), Dodecylazacycloheptanone, SEPA® such as described in US Patent 4,861,764 (e.g. 2-n-nonyl-1,3-dioxolane), and mixtures thereof.

Most preferred is diethylene glycol monoethyl ether (available from Gattefosse under the tradename Transcutol).

It is preferred that the compositions herein comprise from about 0.1% to about 99%, preferably from about 0.1% to about 90%, more preferably from about 5% to about 90%, even more preferably from about 15% to about 75%, by weight of skin penetration enhancer.

It is preferred that the ratio of photosensitizer to skin-penetration enhancer is from about 1:20 to about 1:10000 , more preferably from about 1:60 to 1:300, on the basis of percentages by weight of total composition.

It is highly preferred that the compositions of the present invention have a viscosity at 20°C of from about 50 cps to about 50000 cps, more preferably from about 500 cps to about 40000 cps, even more preferably from about 5000 cps to about 30000 cps.

Solubilizer

It is highly preferred that the compositions herein comprise a solubilizer. This is especially true when the photosensitizer is hydrophobic. Some solubilizers are also penetration enhancers and it is preferred that the compositions herein comprise a penetration enhancer that is also a solubilizer for the photosensitizer.

Preferably the solubilizer is selected from glycol ethers, polyethylene glycol, polyethylene glycol derivatives, propylene glycol, propylene glycol derivatives, fatty alcohols, aromatic alcohols, propylene glycol, glycerols, oils, surfactants, glucosides, and mixtures thereof.

More preferably the solubilizer is selected from diethylene glycol monoethyl ether (Transcutol®), polyethylene glycol of average molecular weight from 100 to 5000, triethylene glycol, tetraethylene glycol, pentaethylene glycol, hexaethylene glycol, septaethylene glycol, octaethylene glycol, propylene glycol, propylene glycol mono- and diesters of fats and fatty acids (e.g. propylene glycol monocaprylate, propylene glycol monolaurate), benzyl alcohol, glycerol, oleyl alcohol, mineral oil, lanolin/lanolin derivatives, petrolatum or other petroleum products suitable for application to the skin, propylene glycol mono- and diesters of fats and fatty acids, macrogols, macrogolglycerides or polyethylene glycol glycerides and fatty esters (e.g. stearoyl macrogolglycerides, oleoyl macrogolglycerides, lauroyl macrogolglycerides, linoleoyl macrogolglycerides), ethoxylated castor oil (e.g. Cremophor – a polyoxyl hydrogenated castor oil), C6-C30 triglycerides, natural oils, glucosides (e.g. cetearyl glucoside), surfactants, and mixtures thereof.

More preferable the solubilizer is selected from diethylene glycol monoethyl ether (Transcutol®), PEG-200, oleyl alcohol, and mixtures thereof.

It is preferred that the compositions herein comprise from about 0.1% to about 99%, more preferably from about 1% to about 75%, by weight of solubilizer.

Viscosity Modifying Agents

The compositions herein preferably comprise a viscosity modifying agent. Preferred viscosity modifiers are selected from polyethylene glycols, acrylic acid-based polymers (carbopol polymers or carbomers), polymers of acrylic acid crosslinked with allyl sucrose or allylpentaerythritol (carbopol homopolymers), polymers of acrylic acid modified by long chain (C10-C30) alkyl acrylates and crosslinked with allylpentaerythritol (carbopol copolymers), poloxamers also known

as pluronics (block polymers; e.g. Poloxamer 124, 188, 237, 338, 407), waxes (paraffin, glyceryl monostearate, diethylene glycol monostearate, propylene glycol monostearate, ethylene glycol monosterate, glycol stearate), hard fats (e.g. Saturated C8-C18 fatty acid glycerides), xantham gum, polyvinyl alcohol, solid alcohols, and mixtures thereof. More preferably the viscosity modifiers are selected from high molecular weight polyethylene glycols, especially PEG-3350.

Optional Ingredients

The compositions herein may comprise a variety of optional components. Any suitable ingredient may be used herein but typically these optional component will render the compositions more cosmetically acceptable or provide additional usage benefits. Some examples of preferred optional ingredients include, but are not limited to, emulsifiers, humectants, emollients, surfactants, oils, waxes, fatty alcohols; dispersants, skin-benefit agents, pH adjusters, dyes/colourants, analgesics, perfumes, preservatives, and mixtures thereof.

Examples of suitable preservatives include but are not limited to parabens, benzyl alcohol, quaternium 15, imidazolidyl urea, disodium EDTA, methylisothiazoline, alcohols, and mixtures thereof. Examples of suitable emulsifiers include but are not limited to waxes, sorbitan esters, polysorbates, ethoxylated castor oil, ethoxylated fatty alcohols, macrogolglycerides or polyethylene glycol glycerides and fatty esters (e.g. stearoyl macrogolglycerides, oleoyl macrogolglycerides, lauroyl macrogolglycerides), esters of saturated fatty acids (e.g. diethylene glycol parmitostearate), macrogols of cetostearyl ether (e.g. macrogol-6-cetostearyl ether), polymers of high molecular weight, crosslinked acrylic acid-based polymers (carbopols or carbomers) , and mixtures thereof. Examples of suitable emollients include but are not limited to propylene glycol dipelargonate, 2-octyldodecyl myristate, non-polar esters, triglycerides and esters (animal and vegetable oils), lanolin, lanolin derivatives, cholesterol, glucosides (e.g. cetearyl glucoside), pegylated lanolin, ethoxylated glycerides, and mixtures thereof. Examples of suitable surfactants include but are not limited to sorbitan esters, polysorbates, sarcosinates, taurate, ethoxylated castor oil, ethoxylated fatty alcohols, ethoxylated glycerides, caprylocaproyl macrogol-8 glycerides, polyglyceryl-6 dioleate, and

mixtures thereof. Examples of suitable oils include but are not limited to propylene glycol monocaprylate, medium chain triglycerides (MCT), 2-octyl-dodecyl myristate, cetearyl ethylhexanoate, and mixtures thereof. Examples of suitable fatty alcohols include but are not limited to cetostearyl alcohol, cetyl alcohol, stearyl alcohol, and mixtures thereof.

Also useful in the compositions herein are lipids and triglycerides (e.g. concentrates of Seed Oil Lipids, Concentrates of Marine Oil Lipids, high purity triglycerides and esters), alkyl ether sulfates, alkyl polyglycosides, alkylsulfates, amphoterics cream bases, and mixtures thereof.

A preferred embodiment of the present invention comprises green-porphyrin photosensitizer, low molecular weight PEG such as PEG200, diethylene glycol monoethyl ether (Transcutol®), high molecular weight PEG such as PEG3350 and fatty alcohol such as oleyl alcohol. While not wishing to be bound by theory it is believed that the PEG3350 acts as a viscosity modifier while the Transcutol, PEG 200, and oleyl alcohol act to deliver the photosensitizer through the stratum corneum.

Method of Use

The present invention also relates to a method of using a compositions as described hereinabove. Said method comprises:

(i) applying to the skin a composition comprising a photosensitizing agent and a carrier wherein the carrier comprises a skin-penetration enhancer,

(ii) allowing time for at least some of the photosensitizer to penetrate through the stratum corneum,

(iii) washing the skin to which the composition has been applied, and

(iv) irradiating with activation energy at a wavelength appropriate to activate the photosensitizer.

The washing step can be performed with any suitable substance.

The washing step can be performed using a composition comprising at least one of the ingredients of the carrier. Preferably, the wash composition comprises two or more, more preferably all, of the ingredients of the carrier. It is preferred that the levels of ingredient(s) in the wash composition are at the same or similar levels as in the carrier.

While not wishing to be bound by theory, it is believed that the washing step removes excess photosensitizer which might otherwise mask the target preventing the activation energy from reaching the target. The utilization of a composition similar to the carrier is believed to aid with the penetration of the photosensitizer composition through the creation of a concentration gradient.

Process

The present compositions can be made by any suitable process. Preferably, the photosensitizer is lyophilized. A preferred process for production of the present compositions comprises:

a) Preparation of lyophilized photosensitizer,
b) Manufacture of base composition comprising a skin penetration enhancer and, optionally, a solubilizer,
c) Addition of the photosensitizer to the base with stirring.

In an alternative process the photosensitizer is first dissolved in a solubilizer with heating. As mentioned above it is preferred that the solubilizer is also a skin-penetration enhancer. After cooling any remaining ingredients are added.

Method of Treatment

The compositions of the present invention may be used for promoting hair growth. The present method comprises applying a composition of the present invention to a suitable target and activating the photosensitizing agent. Typically, from about 0.1g to about 50g, preferably from about 1g to about 10g, of the composition is applied to the target. The activation energy can be from an suitable energy source.

The compositions of the present invention can be used for the treatment of androgenetic alopecia. The present method comprises applying a composition of the present invention to a suitable target and activating the photosensitizing agent. Typically, from about 0.1g to about 50g, preferably from about 1g to about 10g, of the composition is applied to the target. The activation energy can be from an suitable energy source.

The compositions of the present invention can be used for the treatment of alopecia areata. The present method comprises applying a composition of the present invention to a suitable target and activating the photosensitizing agent. Typically, from about 0.1g to about 50g, preferably from about 1g to about 10g, of the composition is applied to the target. The activation energy can be from an suitable energy source.

The compositions of the present invention can be used for the treatment of skin cancers. The present method comprises applying a composition of the present invention to a suitable target and activating the photosensitizing agent. Typically, from about 0.1g to about 50g, preferably from about 1g to about 10g, of the composition is applied to the target. The activation energy can be from an suitable energy source.

The compositions of the present invention can be used for the treatment of acne. The present method comprises applying a composition of the present invention to a suitable target and activating the photosensitizing agent. Typically, from about 0.1g to about 50g, preferably from about 1g to about 10g, of the composition is applied to the target. The activation energy can be from an suitable energy source.

The compositions of the present invention can be used for the treatment of psoriasis. The present method comprises applying a composition of the present invention to a suitable target and activating the photosensitizing agent. Typically, from about 0.1g to about 50g, preferably from about 1g to about 10g, of the composition is applied to the target. The activation energy can be from an suitable energy source.

The compositions of the present invention can be used for the treatment of atopic dermatitis. The present method comprises applying a composition of the present invention to a suitable target and activating the photosensitizing agent. Typically, from about 0.1g to about 50g, preferably from about 1g to about 10g, of the composition is applied to the target. The activation energy can be from an suitable energy source.

The compositions of the present invention can be used for the treatment of endometrial ablation. The present method comprises applying a composition of the present invention to a suitable target and activating the photosensitizing agent. Typically, from about 0.1g to about 50g, preferably from about 1g to about 10g, of the composition is applied to the target. The activation energy can be from an suitable energy source.

Examples

It will be understood that the following embodiments of the present invention are intended to be illustrative of some of the possible applications or principles. Various modifications may be made by the skilled person without departing from the true spirit and scope of the invention.

	Example 1 (wt%)	Example 2 (wt%)	Example 3 (wt%)	Comparative Example (wt%)
QLT0074	0.5	0.25	0.75	0.5
PEG-200	54	50	58	54
Transcutol®[1]	20	24	16	0
PEG-3350	15.5	10	15.5	15.5
Oleyl Alcohol	10	15.75	10	30

[1] Diethylene glycol monethyl ether available from Gattefosse Canada Inc., Baie D'Urfé, Québec, H9X 2T3, Canada

The above compositions were prepared in the following way:

a) Preparation of cryodessicated photosensitizer – the QLT0074 is dissolved in Glacial Acetic Acid. The solution is then frozen in a dry ice/isopropanol bath and the acetic acid is removed by lyophilization. The resultant material is a fine fluffy powder which goes into topical solution easily.

b) Manufacture of base – the PEG 200 is warmed to 80-90 °C with stirring. PEG 3.35K is added with stirring followed by oleyl alcohol, then where present the transcutol®. Stirring is continued until solution is clear.

c) Addition of photosensitizer - base composition is cooled to approx. 50 °C and the photosensitizer is added with stirring. Stirring is continued with cooling until homogeneous paste is achieved. The resulting formulation is checked for the absence of undissolved photosensitizer crystals by phase contrast microscopy.

It was found that Examples 1-3 gave good penetration of the QLT0074 through the stratum corneum while the comparative example did not.

Claims:

1. A composition comprising:
   a) photosensitizer,
   b) skin-penetration enhancer.

2. A composition according to claim 1 wherein the photosensitizer is selected from polypyrrolic macrocycles.

3. A composition according to claim 1 wherein the photosensitizer is selected from green-porphyrins.

4. A composition according to claim 1 where the photosensitizer is present at a level of from 0.0001% to 50%.

5. A composition according to claim 1 wherein the skin-penetration enhancer is selected from glycol ethers, fatty acids, fatty acid esters, glycol esters, glycerides, azones, polysorbates, alcohols, dimethylsulfoxide, and mixtures thereof.

6. A composition according to claim 1 wherein the skin-penetration enhancer is selected from diethylene glycol monoethyl ether, polyethylene glycol of average molecular weight from 200 to 4000, oleyl alcohol, and mixtures thereof.

7. A composition according to claim 1 where the skin-penetration enhancer is present at a level of from about 0.1% to about 90%.

8. A composition according to claim 1 wherein the skin-penetration enhancer is also a solubilizer for the photosensitizer.

9. A composition according to claim 1 wherein the composition comprises a solubiliser selected from diethylene glycol monoethyl ether, polyethylene

glycol of average molecular weight from 200 to 4000, oleyl alcohol, and mixtures thereof.

10. A composition according to claim 1 wherein the composition has a viscosity at 20°C of from about 50 cps to about 50000 cps.

11. A composition comprising green-porphyrin photosensitizer, low molecular weight polyethylene glycol, diethylene glycol monoethyl ether, high molecular weight polyethylene glycol, and fatty alcohol.

12. The use of a composition according to claim 1 or 11 for application to the skin for the purposes of photodynamic therapy.

13. The use of a composition according to claim 1 or 11 for the photodynamic treatment of androgenetic alopecia, alopecia areata, skin cancers, acne, psoriasis atopic, dermatitis, endometrial ablation, or for promoting hair growth.

14. A method of treating androgenetic alopecia, skin cancers, acne, or for promoting hair growth, said method comprising applying a composition according to claim 1 or 11 to the target tissue and irradiating the target tissue with activation energy of a appropriate wavelength to activate the photosensitizer.

15. A method of photodynamic therapy comprising:

(i) applying to the skin a composition comprising a photosensitizing agent and a carrier wherein the carrier comprises a skin-penetration enhancer,

(ii) allowing time for at least some of the photosensitizer to penetrate through the stratum corneum,

(iii) washing the skin to which the composition has been applied, and

(iv) irradiating with activation energy at a wavelength appropriate to activate the photosensitizer.

16. A process of the manufacture of a composition according to claim 1, said process comprising:

(a) preparing a lyophilized photosensitizer,

(b) manufacturing a base composition comprising a skin penetration enhancer and, optionally, a solubilizer, and

(c) adding the lyophilized photosensitizer to the base with stirring.

INTERNATIONAL SEARCH REPORT

Int[illegible]onal Application No
PCT/CA 02/01734

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K41/00 A61K47/08 A61K47/10 A61K31/40 A61P17/14

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, EMBASE, BIOSIS, MEDLINE, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 350 036 A (LONG ISLAND JEWISH MEDICAL CEN) 10 January 1990 (1990-01-10) the whole document ---	1-16
X	US 4 753 958 A (WEINSTEIN GERALD D ET AL) 28 June 1988 (1988-06-28) abstract column 7, line 27-63 claim 15 ---	1-16
X	US 5 283 255 A (CHOW JACK J ET AL) 1 February 1994 (1994-02-01) cited in the application column 20, line 10-19 examples 17,18 --- -/--	1-16

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
19 February 2003	18/03/2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Skjöldebrand, C

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INTERNATIONAL SEARCH REPORT

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	WO 88 05653 A (PROCTOR PETER H) 11 August 1988 (1988-08-11) page 5, line 1-15 claims 11,12 examples	1-11,16
X	FR 2 693 906 A (VICHY CIE FERMIERE ETABL THERM) 28 January 1994 (1994-01-28) abstract examples	1,2,4,5, 7,8,10
P,X	WO 01 85213 A (UNIV BRITISH COLUMBIA) 15 November 2001 (2001-11-15) page 37, line 10-15 page 42, line 15-24 examples	1-16
P,X	WO 01 85212 A (UNIV BRITISH COLUMBIA) 15 November 2001 (2001-11-15) page 34, line 4-9 page 39, line 14-25 examples	1-16
X	MCCULLOUGH J L ET AL: "DEVELOPMENT OF A TOPICAL HEMATO PORPHYRIN DERIVATIVE FORMULATION CHARACTERIZATION OF PHOTO SENSITIZING EFFECTS IN-VIVO" JOURNAL OF INVESTIGATIVE DERMATOLOGY, vol. 81, no. 6, 1983, pages 528-532, XP009005353 ISSN: 0022-202X abstract	1-16
X	SACCHINI V ET AL: "TOPICAL ADMINISTRATION OF TETRASODIUM-MESO-TETRAPHENYLPORPHINESULFONATE TPPS AND RED LIGHT IRRADIATION FOR THE TREATMENT OF SUPERFICIAL NEOPLASTIC LESIONS" TUMORI, vol. 73, no. 1, 1987, pages 19-24, XP009005337 ISSN: 0300-8916 abstract page 20, column 1, paragraph 1	1-16
X	STEINER ROLF A ET AL: "Rat reproductive performance following photodynamic therapy with topically administered photofrin." HUMAN REPRODUCTION (OXFORD), vol. 10, no. 1, 1995, pages 227-233, XP009005336 ISSN: 0268-1161 abstract	1-16

-/--

INTERNATIONAL SEARCH REPORT

Inte ⁻ ɔnal Application No
PCT/CA 02/01734

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	MONFRECOLA G ET AL: "Topical hematoporphyrin plus UVA for treatment of alopecia areata." PHOTO-DERMATOLOGY. DENMARK DEC 1987, vol. 4, no. 6, December 1987 (1987-12), pages 305-306, XP009005364 ISSN: 0108-9684 page 305, column 1, paragraph 2 ---	1-16
X	YAROSH DANIEL B: "Liposomes in investigative dermatology." PHOTODERMATOLOGY PHOTOIMMUNOLOGY & PHOTOMEDICINE, vol. 17, no. 5, October 2001 (2001-10), pages 203-212, XP009005257 ISSN: 0905-4383 abstract ---	1-16
X	DELMARRE D; HIOKA N; BOCH R; STERNBERG E; DOLPHIN D : "Aggregation studies of benzoporphyrin derivative" CANADIAN JOURNAL OF CHEMISTRY, vol. 79, no. 5-6, 2001, pages 1068-1074, XP009005260 abstract ---	1-5,7,8
A	WO 95 07077 A (DZIEGLEWSKA HANNA EVA ;MALIK ZVI (IL); GIERSKCKY KARL ERIK (NO); P) 16 March 1995 (1995-03-16) abstract claims -----	1-16

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-10, 12-16 (all in part)

Present claims 1-10, relate to a composition defined by reference to a desirable characteristic or property of the ingredients, namely a "photosensitizer" and a "skin-penetration enhancer".
The claims cover all compounds having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the composition by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to a composition wherein the "photosensitizer" is as specified in claims 2-3, and he "skin-penetration enhancers" as specified in claim 6, as well as the general underlying concept. The "skin-penetration enhancers" as specified in claim 5 could not could not be fully serched due to the use of extremely broad terms, such as "fatty acids" and "alcohols".
Method claims 12-15 and process claim 16 have only been searched insofar they refer to the searched compositions.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

national application No.
PCT/CA 02/01734

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 12-15 are directed to a method of treatment of the human body, the search has been carried out and based on the alleged effects of the composition.

2. [X] Claims Nos.: 1-10, 12-16 (all in part)
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

...ormation on patent family members

Inte[illegible]nal Application No
PCT/CA 02/01734

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0350036 A	10-01-1990	US 4925736 A	15-05-1990
		AU 616993 B2	14-11-1991
		AU 3968289 A	05-02-1990
		EP 0350036 A2	10-01-1990
		EP 0375773 A1	04-07-1990
		JP 2503680 T	01-11-1990
		JP 2653387 B2	17-09-1997
		NO 901018 A ,B,	27-04-1990
		WO 9000393 A1	25-01-1990
US 4753958 A	28-06-1988	NONE	
US 5283255 A	01-02-1994	US 4883790 A	28-11-1989
		US 4920143 A	24-04-1990
		US 5171749 A	15-12-1992
		US 5399583 A	21-03-1995
		AT 104859 T	15-05-1994
		AU 618725 B2	09-01-1992
		AU 1038888 A	21-07-1988
		CA 1333442 A1	06-12-1994
		DE 3889231 D1	01-06-1994
		DE 3889231 T2	11-08-1994
		EP 0276121 A2	27-07-1988
		ES 2055735 T3	01-09-1994
		JP 1999536 C	08-12-1995
		JP 6008319 B	02-02-1994
		JP 63277700 A	15-11-1988
		JP 2835294 B2	14-12-1998
		JP 7258262 A	09-10-1995
		MX 9203250 A1	31-07-1992
		US 5095030 A	10-03-1992
		AT 127696 T	15-09-1995
		AT 209650 T	15-12-2001
		AU 638675 B2	08-07-1993
		AU 3825889 A	08-02-1990
		DE 68924215 D1	19-10-1995
		DE 68924215 T2	15-02-1996
		DE 68929351 D1	10-01-2002
		DE 68929351 T2	08-05-2002
		EP 0352076 A2	24-01-1990
		EP 0641796 A1	08-03-1995
		ES 2080745 T3	16-02-1996
		ES 2169060 T3	01-07-2002
		GR 3017426 T3	31-12-1995
		JP 2149519 A	08-06-1990
		JP 7080887 B	30-08-1995
		LU 90718 A9	01-03-2001
		NO 900731 A ,B,	18-01-1991
WO 8805653 A	11-08-1988	AU 1362488 A	24-08-1988
		US 5352442 A	04-10-1994
		WO 8805653 A1	11-08-1988
		US 5472687 A	05-12-1995
		US 5470876 A	28-11-1995
		US 5714482 A	03-02-1998
		US 5716947 A	10-02-1998
		US 5714510 A	03-02-1998
		US 5723502 A	03-03-1998

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter[illegible]onal Application No
PCT/CA 02/01734

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO 8805653 A		US	5728714 A	17-03-1998
		US	6150405 A	21-11-2000
FR 2693906 A	28-01-1994	FR	2693906 A1	28-01-1994
		AT	161726 T	15-01-1998
		AU	4574393 A	14-02-1994
		DE	69316216 D1	12-02-1998
		DE	69316216 T2	16-04-1998
		DE	652763 T1	02-05-1996
		DK	652763 T3	09-02-1998
		EP	0652763 A1	17-05-1995
		ES	2083933 T1	01-05-1996
		WO	9402161 A1	03-02-1994
		GR	96300011 T1	31-03-1996
		GR	3026073 T3	29-05-1998
WO 0185213 A	15-11-2001	AU	5811701 A	20-11-2001
		WO	0185213 A2	15-11-2001
		US	2002061330 A1	23-05-2002
WO 0185212 A	15-11-2001	AU	5809501 A	20-11-2001
		WO	0185212 A2	15-11-2001
		US	2002155089 A1	24-10-2002
WO 9507077 A	16-03-1995	AU	7543794 A	27-03-1995
		WO	9507077 A1	16-03-1995